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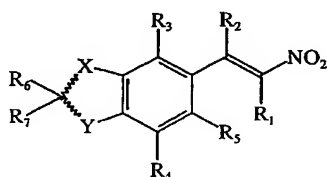
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(54) Title: GROWTH PROMOTION METHOD



(I)



(a)

(57) Abstract: The present invention relates to a method of promoting growth comprising the step of administering an effective amount of a compound of formula (I); in which X and Y are either the same or different and selected from a heteroatom; (a) is a double or single bond depending on the heteroatoms X and Y; R₁ to R₅ are either the same or different and selected from hydrogen or a non-deleterious substituent; and R₆ and R₇ are either the same or different and selected from hydrogen and a non-deleterious substituent or one of R₆ and R₇ are absent when there is a double bond present, pharmaceutically or veterinarily acceptable salts or derivatives, pro-drugs, tautomers and/or isomers thereof to a subject in need thereof.

GROWTH PROMOTION METHODFIELD OF THE INVENTION

5 This invention relates to a growth promotion method and in particular to a method of promoting growth of an animal, more specifically intensively farmed animals, such as, pigs, cows, sheep, chickens, turkeys or fish.

10 BACKGROUND

All references, including any patents or patent applications, cited in this specification are hereby incorporated by reference. No admission is made that any reference constitutes prior art. The discussion of the references states what their authors assert, and the applicants reserve the right to challenge the accuracy and pertinency of the cited documents. It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

A popular method of livestock management is the intensive management system, which dramatically increases the population density of farmed animals and therefore improves the cost efficiency of housing, management and labour compared to less intensive management systems. However, a major consequence of intensive management is the increased opportunity for the development and spread of disease. This disease may be caused by specific pathogens introduced, for example, by errors in practice management, or by opportunistic pathogens in the contaminated and compromising intensively managed environment.

35 Clinical infections can lead to major disease outbreaks with high morbidity and/or mortality. Subclinical infections can interfere with the normal

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metabolic process of an animal. For example, interference with the gastrointestinal function of an animal can interfere with its normal eating habits. This results in poor growth and feed efficiencies by the animal, which in turn results in less efficient animal production.

Most additives can, but do not always, improve feed use and rate of live weight gain by 3 to 8 percent. However, as the additives increase the cost of a diet, their inclusion will only be cost effective if the improved performance covers the cost of the additive and the same improvement could not have been obtained by a less expensive means, such as a change in management system or an improved strain of animal.

Current feed additives approved for use in livestock diets are generally administered at 1 to 175 mg/kg feed. Many feed additives must be withdrawn from the diet before slaughter in order to minimise the presence of residues of the additive in the meat of the animal when consumed.

Current additives used to promote growth of animals include the administration of antibiotics, vitamins and minerals including copper and arsenicals, and hormone regulation therapies. Classic examples include use of the arsenicals to control swine dysentery, coccidiostats to control coccidiosis in poultry, and vitamins which compensate for vitamin deficiencies. However, feeding these molecules to animals which will be consumed by humans often raises concerns on the effect to both humans and the environment as a result of the development of antibiotic resistant bacteria and the residues remaining in the animal and in the soil. For example, there has been evidence of copper residues in pig livers and also in soils treated with pig slurry.

The development of antibiotic resistance in organisms is another major concern to consumers and compromises the ability of many widely used antibiotics to treat serious infections in humans. Not all antibiotics

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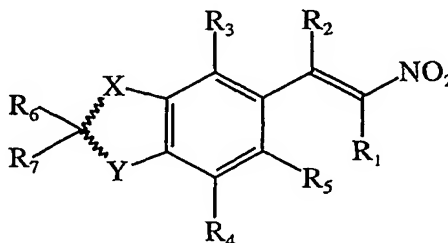
promote growth. For example, broad spectrum antibiotics are not generally used for this purpose. Therefore, the development of a growth promoting agent which leaves a minimal or no detectable residue is also of concern to consumers. Allergic reactions which occur as a result of consuming specific additives is known to occur. The effect of hormone supplements on consumers is of further concern and several hormone treatment programs in poultry and beef cattle have been restricted. There is increasing pressure from consumers to restrict the use of many compounds. In the European Economic Community, for example, non-authorised additives include tetracyclines, penicillins and cephalosporins, aminoglycosides, macrolides, sulfonamides and trimethoprim, nitrofurans except nitrovin, arsenicals, hormones and anti-hormones.

A requirement accordingly exists for growth promoting agents which leave minimal residues in animals to which they have been administered and in the environment.

SUMMARY OF INVENTION

We have now found that certain substituted nitrostyrene compounds have improved growth promotant activity, require low dosage, result in low tissue levels, and have low oral toxicity.

In a first aspect, the present invention provides a method of promoting growth comprising the step of administering an effective amount of a compound of formula I:



I

in which

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X and Y are either the same or different and selected from a heteroatom;

is a double or single bond depending on the heteroatoms X and Y;

5 R₁ to R₅ are either the same or different and selected from hydrogen or a non-deleterious substituent; and

R₆ and R₇ are either the same or different and selected from hydrogen and a non-deleterious substituent
10 or one of R₆ and R₇ are absent when there is a double bond present,

pharmaceutically or veterinarily acceptable salts or derivatives, pro-drugs, tautomers and/or isomers thereof to a subject in need thereof.

15 The present invention also provides the use of the compound of formula I in promoting growth of a subject.

The present invention further provides the use of the compound of formula I in the manufacture of a
20 medicament or feed for promoting growth of a subject.

The present invention still further provides the compound of formula I for use in promoting growth of a subject.

In a second aspect, the present invention
25 provides a composition for promoting growth in a subject, which comprises the compound of formula I and a carrier.

When the composition is to be administered to a human or animal, it is preferably in the form of a pharmaceutical or veterinary composition comprising the
30 compound of formula I and a pharmaceutically or veterinarily acceptable carrier.

Alternatively, the composition may be administered in the form of a feed for promoting growth in a subject comprising the compound of formula I.

35 In a third aspect, the present invention provides a growth promoting agent or a nutritional supplement comprising the compound of formula I.

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The present invention also provides use of the compound of formula I as a growth promoting agent or nutritional supplement.

5 DETAILED DESCRIPTION OF THE INVENTION

In the subject specification, except where the context requires otherwise due to express language or necessary implication, the words "comprise" or variations such as "comprises" or "comprising" are used in an
10 inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It must be noted that, as used in the subject
15 specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a single compound, as well as two or more compounds; and so forth.


20 In the compound of formula I, preferably X and Y are either the same or different and selected from O and N, more preferably both X and Y are oxygen.

Preferably R₁ and R₂ are either the same or different and selected from hydrogen, hydroxy, halogen and
25 optionally substituted C₁₋₆ alkyl.

R₃ to R₅ are preferably either the same or different and selected from hydrogen, hydroxy, halogen, nitro, C₁₋₆ alkoxy and optionally substituted C₁₋₆ alkyl.

Preferably halogen is chlorine or bromine.

30 The E isomer of the compounds of formula I is preferred.

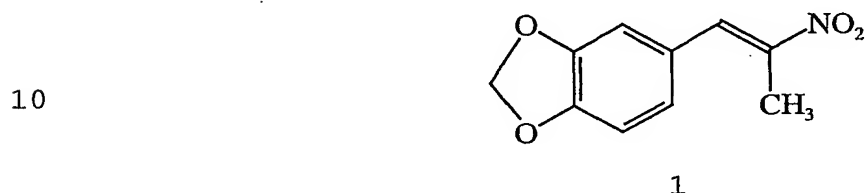
Particularly preferred are compounds of the formula I in which X, Y, , R₆ and R₇ are as defined above; R₁ and R₂ are either the same or different and selected
35 from hydrogen, hydroxy, Cl, Br and C₁₋₄ alkyl; and R₃ to R₅ are either the same or different and selected from hydrogen, hydroxy, Cl, Br, nitro, C₁₋₄ alkoxy and C₁₋₄

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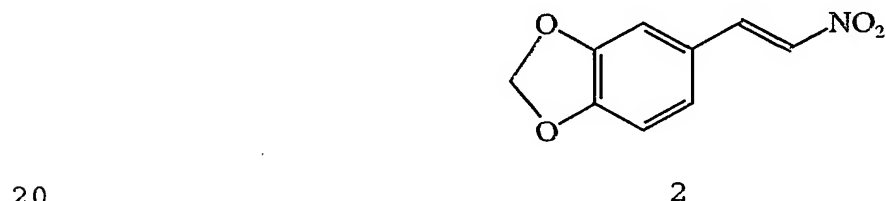
alkyl.

Specific examples of the compounds of the present invention are as follows:

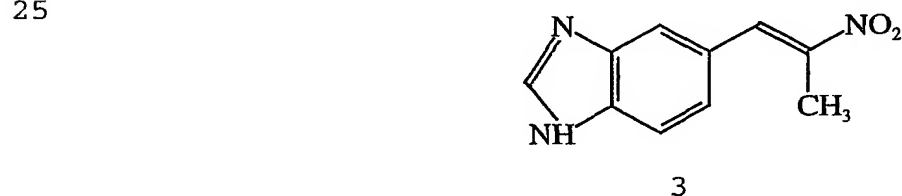
- 5 (1) X and Y are O, R₁ is methyl and R₂ and R₃ are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene) (hereinafter referred to as "Iksin")



- 15 (2) X and Y are O and R₁ to R₃ are hydrogen (3,4-methylenedioxy-β-nitrostyrene)

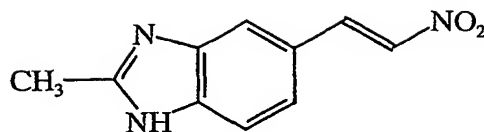


- 25 (3) X is N, Y is NH, R₁ is methyl and R₂ and R₃ are hydrogen (benzimidazole-5-β-nitropropylene)



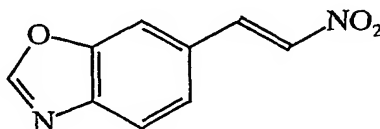
- (4) X is N, Y is NH, R₁ is hydrogen, R₂ is methyl and R₃ is absent (2-methyl benzimidazole-5-β-nitroethylene)

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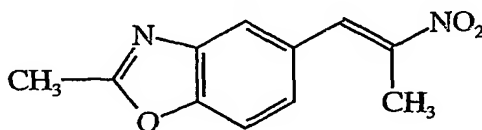
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- (5) X is O, Y is N, R₁ and R₂ are hydrogen and R₃ is absent (benzoxazole-5-β-nitroethylene)



5

- (6) X is N, Y is O, R₁ and R₂ are methyl and R₃ is absent (2-methyl benzoxazole-5-β-nitropropylene)



6

By "pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, hydrate, ester, amide, active metabolite, analogue, residue or any other compound which is not biologically or otherwise undesirable and induces the desired pharmacological and/or physiological effect.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of

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pharmaceutically acceptable cations such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium; acid addition salts of pharmaceutically acceptable inorganic acids such as hydrochloric, orthophosphoric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic and hydrobromic acids; or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, trihalomethanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "pro-drug" is used herein in its broadest sense to include functional derivatives of the compound of formula I which are readily convertible *in vivo* to the compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985.

The term "tautomer" is used herein in its broadest sense to include compounds of formula I which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound.

The term "isomer" is used herein in its broadest sense and includes structural, geometric and stereo isomers. As the compound of formula I may have one or more chiral centres, it is capable of existing in enantiomeric forms.

The term "heteroatom" denotes O, N or S.

The term "non-deleterious substituent" is used herein in its broadest sense and refers to a substituent which does not have a deleterious effect on the growth promoting property of the compound. Examples include

5 alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl,

10 amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy,

15 heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy mercapto, alkylthio, arylthio, acylthio and phosphorus-containing compounds.

Particularly suitable non-deleterious

20 substituents are alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, nitroalkyl, nitroalkenyl and nitroalkynyl.

In a preferred embodiment the non-deleterious

25 substituents are C₁₋₆ alkyl, halo, hydroxy, C₁₋₆ alkoxy and nitro.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably chlorine and bromine.

The term "alkoxy" is used herein in its broadest

30 sense and refers to straight chain, branched chain or cyclic oxy-containing radicals each having alkyl portions, preferably C₁₋₆ alkyl, more preferably C₁₋₄ alkyl. Examples of such alkoxy groups are methoxy, ethoxy, propoxy, butoxy and t-butoxy.

35 The terms "C₁₋₄ alkyl" or "C₁₋₆ alkyl" used either alone or in compound words such as "optionally substituted C₁₋₄ or C₁₋₆ alkyl" refer to straight chain, branched chain

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or cyclic hydrocarbon groups having from 1 to 6 carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "subject" as used herein refers to any subject in which the promotion of growth is desired. The subject may have or be at risk of having a disease or condition which requires growth promotion. The subject may be an animal or a human. While it is particularly contemplated that the compounds of the invention are suitable for treatment of domestic animals such as horses, ponies, donkeys, mules, llama, alpaca, pigs, cattle, sheep, birds and fish, or zoo animals such as primates, felids, canids, bovids, and ungulates, they are also applicable to use in humans and companion animals such as dogs and cats.

Preferably the animal is a mammal, bird or fish.

Suitable mammals include members of the orders Primates, Rodentia, Lagomorpha, Cetacea, Carnivora, Perissodactyla and Artiodactyla. Members of the orders Perissodactyla and Artiodactyla are particularly preferred because of their economic importance.

For example, Artiodactyla comprises approximately 150 living species distributed through nine families: pigs (Suidae), peccaries (Tayassuidae), hippopotamuses (Hippopotamidae), camels (Camelidae), chevrotains (Tragulidae), giraffes and okapi (Giraffidae), deer (Cervidae), pronghorn (Antilocapridae), and cattle, sheep, goats and antelope (Bovidae). Many of these animals, such as goats, sheep, cattle and pigs have very similar biology and share high degrees of genomic homology.

The order Perissodactyla comprises horses and donkeys, which are both economically important and closely related. Indeed, it is well known that horses and donkeys interbreed.

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Preferably the mammal is a pig, cow or sheep.

Examples of birds include members of the order Anseriformes, which includes geese and ducks; Galliformes, which includes chickens, turkeys, quail, pheasants, guinea
5 fowl and pea fowl; and Columbiformes, which includes pigeons and doves. Preferably the bird is a chicken, turkey, duck or goose.

Examples of fish include Clupeiforms, Perciformes, Gadiformes, Pleuronectiformes, Cypriniformes,
10 Crustaceans and Molluscs.

In a preferred embodiment, the subject is an animal, more preferably an intensively farmed animal such as mammals, for example, pigs, cows or sheep; birds, for example, chickens such as broiler chickens, turkeys, ducks
15 or geese; or fish.

As used herein, the term "farmed intensively" means farmed with the aim of achieving maximum production within a limited area.

Without wishing to be bound by theory, it is
20 believed that compounds of formula I act to promote the growth of a subject by inhibiting the growth of pathogens in the gastrointestinal tract as well as having a direct effect of feed utilisation.

The promotion of growth may be determined by any
25 suitable known method. In a preferred method, promotion of growth is determined by an increase in the weight, length, and/or height or a decrease in food intake, a reduction in time to reach marketable weight and/or instance of microbial infection of the subject as compared
30 to a control subject. In a more preferred method, promotion of growth is determined by an increase in the weight of a subject as compared to a control subject.

It will be clearly understood that the terms "promotion of growth" and "promoting growth" mean the
35 increase of growth of a subject when compared to a control subject.

As used herein, the term "control subject" means

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a subject of the same species, age and sex as the subject whose growth is being promoted however, the control subject has not been administered the compound of formula I.

5 As used herein, the term "effective amount" is meant an amount of a compound of the present invention effective to yield the desired growth promoting activity.

 The specific "effective amount" will, obviously, vary with such factors as the particular condition being
10 treated, the physical condition of the subject, the type of subject being treated, the duration of the treatment, the nature of concurrent therapy (if any), the specific formulations employed and the structure of the compound or its derivatives.

15 Dosage levels of the compound of formula I of the present invention may be of the order of up to about 1g per kilogram body weight. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the
20 animal treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain up to about 1 g of an active compound with an appropriate and convenient amount of carrier material which may vary from about 5 to about
25 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient. When used in a feed, the amount of active ingredient will be about 10 ppm to about 100 ppm.

30 Optionally the compounds of the invention are administered in a divided dose schedule, such that there are at least two administrations in total in the schedule. Administrations are given preferably at least every two hours for up to four hours or longer; for example the
35 compound may be administered every hour or every half hour. In one preferred embodiment, the divided-dose regimen comprises a second administration of the compound

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of the invention after an interval from the first administration sufficiently long that the level of active compound in the blood has decreased to approximately from 5-30% of the maximum plasma level reached after the first administration, so as to maintain an effective content of active agent in the blood. Optionally one or more subsequent administrations may be given at a corresponding interval from each preceding administration, preferably when the plasma level has decreased to approximately from 10-50% of the immediately-preceding maximum.

The compounds of the present invention may additionally be combined with other molecules to provide an operative combination. It is intended to include any chemically compatible combination of pharmaceutically- or veterinarily-active agents, as long as the combination does not eliminate the activity of the compound of formula I. It will be appreciated that the compound of the invention and the other molecule(s) may be administered separately, sequentially or simultaneously.

Other molecules which may be used to promote growth include other antimicrobials in reduced amounts, vitamins and/or minerals.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the compound of formula I to a subject. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Each carrier must be pharmaceutically or veterinarily "acceptable" in the sense of being compatible with other ingredients of the composition and non-injurious to a subject.

The pharmaceutically or veterinarily acceptable carrier is preferably an organic solvent such as acetone, benzene, acetonitrile, DMSO or an alcohol, for example, methanol or ethanol. While the compounds of formula I show a poor solubility in water, when water is combined with an organic solvent a stable mixture is formed.

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Carriers suitable for use in the preparation of the feed supplements include alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, sodium chloride, corn meal, cane molasses, urea, bone meal, fish meal, 5 corncob meal, calcium chloride, vegetable or plant oils such as olive oil or canola oil and other similar materials. Use of the carriers in feed supplements promote uniformity of distribution of the compound of formula I in the finished feed into which the supplement 10 is blended. It thus performs an important function by ensuring proper distribution of the compound of formula I throughout the feed.

It will be understood that the compound of formula I can be administered by any means. Preferably, 15 the compound is administered orally, topically, or parentally, more preferably orally, most preferably orally in the form of a feed. The compound of formula I may be administered orally, topically, or parenterally in dosage unit formulations containing conventional non-toxic 20 pharmaceutically or veterinarily acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous injections, aerosol for administration to lungs or nasal cavity, intravenous, intramuscular, intrathecal, intracranial, injection or 25 infusion techniques.

The present invention also provides suitable topical, oral and parenteral pharmaceutical or veterinary formulations for use in the methods of the present invention. The compounds of the present invention may be 30 administered orally as a feed, or as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. As used herein, the word "feed" means food or drink.

The composition for oral use may contain one or 35 more agents selected from the group of sweetening agents, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically or veterinarily

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elegant and palatable preparations. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharin. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable preservatives include sodium benzoate, vitamin E, alphatocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate. The tablets contain the active ingredient in admixture with non-toxic pharmaceutically or veterinarily acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

The compound of formula I as well as the pharmaceutically or veterinarily active agent useful in the method of the invention can be administered, for in vivo application, parenterally by injection or by gradual perfusion over time independently or together.

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Administration may be intravenously, intraarterial, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally or infusion by, for example, osmotic pump. For in vitro studies the agents may be
5 added or dissolved in an appropriate biologically acceptable solvent or buffer and added to a cell or tissue.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions,
10 suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable or plant oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or
15 suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those
20 based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, other antimicrobials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

Generally, the terms "treating", "treatment" and
25 the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or sign or symptom thereof, and/or may be therapeutic in
30 terms of a partial or complete cure of a disease. "Treating" as used herein covers any treatment of, or prevention of disease in a subject, and includes: (a) preventing the disease from occurring in a subject that may be predisposed to the disease, but has not yet been
35 diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving or ameliorating the effects of the disease, i.e., cause

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regression of the effects of the disease.

The invention includes various pharmaceutical or veterinary compositions useful for ameliorating disease. The pharmaceutical or veterinary compositions according to one embodiment of the invention are prepared by bringing the compound of formula I, analogues, derivatives or salts thereof, or combinations of the compound of formula I and one or more pharmaceutically or veterinarily active agents into a form suitable for administration to a subject using carriers, excipients and additives or auxiliaries. Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial agents, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 20th ed. Williams & Williams (2000), the British National Formulary, 43rd edition (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2000), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical or veterinary composition are adjusted according to routine skills in the art. See Goodman and Gilman's The Pharmacological Basis for Therapeutics (7th ed., 1985).

The pharmaceutical or veterinary compositions are preferably prepared and administered in dose units. Solid dose units may be tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature

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and severity of the disorder, age and body weight of the animal, different daily doses can be used. Under certain circumstances, however, higher or lower daily doses may be appropriate. The administration of the daily dose can be
5 carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals.

The pharmaceutical or veterinary compositions
10 according to the invention may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the disease and the weight and general state of the subject. Typically, dosages used *in vitro* may
15 provide useful guidance in the amounts useful for *in situ* administration of the pharmaceutical or veterinary composition, and animal models may be used to determine effective dosages for the promotion of growth. Various considerations are described, e.g., in Langer, Science,
20 249: 1527, (1990). Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules
25 wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the
30 manufacture of aqueous suspension. Such excipients may be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which may be
35 (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a

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condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

10 The pharmaceutical or veterinary compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been
15 mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are
20 water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition,
25 fatty acids such as oleic acid find use in the preparation of injectables.

 The compounds of formula I may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar
30 vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

 The compounds of formula I may preferably be presented for use in the form of veterinary compositions,
35 which may be prepared, for example, by methods that are conventional in the art. Examples of such veterinary compositions include those adapted for:

- 20 -

oral administration, external application, for example drenches (e.g. aqueous or non-aqueous solutions or suspensions); tablets or boluses; powders, granules or pellets for admixture with feed stuffs; pastes for application to the tongue;

5 parenteral administration for example by subcutaneous, intramuscular or intravenous injection, e.g. as a sterile solution or suspension; or (when appropriate) by intramammary injection where a suspension or solution is

10 introduced in the udder via the teat;

topical applications, e.g. as a cream, ointment or spray applied to the skin; or

intravaginally, e.g. as a pessary, cream or foam.

15 BRIEF DESCRIPTION OF THE DRAWINGS

In the examples, reference will be made to the accompanying drawings in which:

Figure 1 is a graph showing plasma levels of Iksin in chicks after treatment with Iksin at 100 µg/g in DMSO and at 400 µg/g in distilled water/Tween20; and

20

Figure 2 is a graph showing the average percentage weight increase in chicks after single dosing with Iksin at 12 µg/g in DMSO, 100 µg/g in DMSO, 200 µg/g in distilled water/Tween20 and 400 µg/g in distilled

25 water/tween20 compared to untreated chicks.

EXAMPLES

The invention will now be described in detail by way of reference only to the following non-limiting

30 examples.

Example 1 - Determination of dose range

Day-old chicks were orally administered Iksin in DMSO at 100 µg/g, 125 µg/g, 150 µg/g and 200 µg/g body weight and in Distilled Water (DW)/5% Tween-20 at 100

35 µg/g, 200 µg/g, 400 µg/g and 500 µg/g body weight.

The maximum tolerated oral dose of Iksin for

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day-old broiler chicks was 200 µg/g Iksin/DMSO and ≥500 µg/g in DW/T20.

Very little Iksin was absorbed from a single oral dosing. Iksin blood levels for doses of 12 µg/g DMSO or 200 µg/g DW were below the limits of detection. At 100 µg/g DMSO and 400 µg/g DW peak levels of 850 ng/g were observed at 48 h (Figure 1).

Effect on chick growth

Treatment with all doses and formulations of Iksin resulted in increased weight gain in chicks 4 days after a single treatment (Figure 2). Chicks treated with Iksin 100 µg/g DMSO showed a 32% increase in weight gain over the group of control chicks. Treatment with Iksin 12 µg/g DMSO, 200 and 400 µg/g DW/T20 gave a mean weight gain of 17%.

Conclusions

Oral administration of Iksin, formulated both in water and DMSO, is effective in promoting chick growth and is poorly absorbed with low tissue residues. It is anticipated that the results observed in the chicks will also be observed in other animals and humans.

Example 2 - Repeat poultry trial

Objective

To investigate the potential of Iksin as a performance enhancing feed additive for broiler chickens and to determine some safety criteria for its use.

Purpose of trial

The purpose of this trial is to compare the performance of Iksin supplemented feed against negative control feed (no additive) and positive control feed (Zn bacitracin).

The parameters to be measured are

- 22 -

- (i) weight gain and feed conversion rates at weekly intervals;
- (ii) pathogen colonisation in the gastrointestinal tract with *Salmonella* and *Campylobacter* by cloacal swab during rearing and by caecum contents at time of processing;
- (iii) the residue of Iksin in breast muscle tissue, fat and liver at time of processing and after 5 days withdrawal; and
- (iv) the level of residues in faeces and broiler litter at time of processing and after 5 days withdrawal.

Trial protocol and methods

15 **Manufacture of rations**

Standard no-additive rations of Broiler Starter and Grower-Finisher Feeds (Ridley) supplemented with Iksin in canola oil and Zn bacitracin (commercial Albac 150) at the concentration recommended by the manufacturer will be prepared by Longerenong Agricultural College.

Chickens

720 1-day old commercial broiler chicks from Hazeldene Bendigo.

25

Treatment groups

Three treatment groups (240 birds each) with 4 replicates (60 birds each)

- 1 rations supplemented with Iksin at 50 mg/kg
- 2 rations supplemented with Zn bacitracin
- 3 rations with no additives

OR

- 35 Six treatment groups of 2 replicates each (or 3 replicates + 1)

1a Iksin 50 mg/kg + old litter

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- 1b Iksin 50 + new litter
- 2a Zn bacitracin + old litter
- 2b Zn bacitracin + new litter
- 3a No additives + old litter
- 5 3b No additives + new litter

Broiler chick management

Birds will be housed according to the industry standard for commercial broiler flocks spatial requirements (0.67 sq ft/bird) and environmental conditions.

Each replicate will be separately housed with separate feed and water supplies.

Feed and water will be available *ad libitum*.

Pens will be seeded with broiler litter (16 weeks old) from a commercial rearing shed at Longerenong.

This litter will be assayed for presence of *Clostridium perfringens*, *Salmonella enterica* and *Campylobacter* spp to confirm contamination level.

Broiler litter will be handled according to commercial industry practice.

Iksin treated birds and litter will be destroyed to waste according to environmental standards.

Untreated birds and positive control birds will be processed as broilers for human consumption.

Birds for serial monitoring

Five chicks from each replicate in each treatment group will be randomly selected for the collection of specific data throughout the study.

Specific data

- a) Measurement of individual weight gain at 0, 14, 28 and 42 days (or slaughter);
- b) Collection of cloacal swabs at 0, 14, 28, 42 days (or slaughter) for microbiological culture for the presence of *Campylobacter* and *Salmonella*;

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c) Collection of breast muscle, liver and fat tissue at slaughter from Iksin treated birds + samples of broiler litter for measurement of Iksin residues;

d) Collection of breast muscle, liver and fat tissue + samples of broiler litter at 5 days post-withdrawal for measurement of Iksin residues;

e) Collection of faecal samples from Iksin treated birds for assay for Iksin;

f) Collection of caecal contents and caecal tissue to determine colonisation and invasion respectively with *Campylobacter* and *Salmonella* (mean viable count per treatment group).

General data

a) Record of feed consumed between 0, 14, 28, 42 days (or slaughter) by weighback of feed in hoppers.

b) Observation for appearance, behaviour and general health and well-being.

c) Record of morbidity (deaths + unfit culls) and any gross pathology data.

Analysis of data

Weight gain and feed efficiency between treatment groups will be compared.

Pathogen colonisation rate in sentinel birds from all treatment groups will be determined by presence/absence of pathogens in cloacal samples.

The effect of Iksin treatment on *Campylobacter* colonisation (caecal contents) and invasion (caecal tissue) at slaughter will be compared to controls of the treatment group mean viable counts.

Expected outcomes

The trial should show:

(i) whether there is a weight gain advantage over negative control birds at specific intervals and at time of processing;

- 25 -

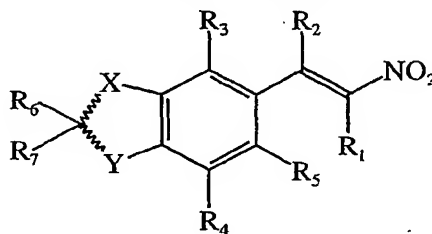
- (ii) how Iksin compares to a treatment regimen previously used in the industry;
- (iii) whether Iksin reduces pathogen incidence (Salmonella and Campylobacter) in the gastrointestinal tract during rearing;
- (iv) whether Iksin reduces pathogen loads or invasion by Campylobacter and salmonella into poultry tissues;
- (v) whether there are any Iksin residues in muscle, fat and liver tissues at slaughter and after withdrawal;
- (vi) the level of Iksin in broiler litter at slaughter and after withdrawal; and
- (vii) whether there is any effect on growth rates of the use of clean versus contaminated litter.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of promoting growth comprising the step of administering an effective amount of a compound of formula I:



I

in which

X and Y are either the same or different and selected from a heteroatom;

- 15 --- is a double or single bond depending on the heteroatoms X and Y;

R₁ to R₅ are either the same or different and selected from hydrogen or a non-deleterious substituent; and

- 20 R₆ and R₇ are either the same or different and selected from hydrogen and a non-deleterious substituent or one of R₆ and R₇ are absent when there is a double bond present,

- 25 pharmaceutically or veterinarily acceptable salts or derivatives, pro-drugs, tautomers and/or isomers thereof to a subject in need thereof.

2. A method according to claim 1, in which the subject is an animal or a human.

30

3. A method according to claim 2, in which the animal is an intensively farmed animal.

4. A method according to claim 3, in which the intensively farmed animal is a mammal, bird or fish.

35

5. A method according to claim 4, in which the

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mammal is a pig, cow or sheep and the bird is a chicken or turkey.

6. A method according to any one of claims 1 to 5,
5 in which X and Y are either the same or different and selected from O and N.


7. A method according to claim 6, in which X and Y
10 are both O.

8. A method according to any one of claims 1 to 7,
in which R₁ and R₂ are either the same or different and
selected from hydrogen, hydroxy, halogen and optionally
substituted C₁₋₆ alkyl.
15

9. A method according to any one of claims 1 to 8,
in which R₃ to R₅ are either the same or different and
selected from hydrogen, hydroxy, halogen, nitro, C₁₋₆
alkoxy and optionally substituted C₁₋₆ alkyl.
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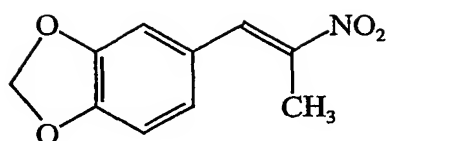
10. A method according to claim 8 or claim 9, in
which the halogen is chlorine or bromine.

11. A method according to any one of claims 1 to 10,
25 in which the compound of the formula I is in the form of an E isomer.

12. A method according to any one of claims 1 to 11,
in which X, Y, , R₆ and R₇ are as defined in claim 1; R₁
30 and R₂ are either the same or different and selected from hydrogen, hydroxy, Cl, Br and C₁₋₄ alkyl; and R₃ to R₅ are either the same or different and selected from hydrogen, hydroxy, Cl, Br, nitro, C₁₋₄ alkoxy and C₁₋₄ alkyl.

35 13. A method according to any one of claims 1 to 12, in which X and Y are O, R₁ is methyl and R₂ and R₃ are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene)

- 28 -

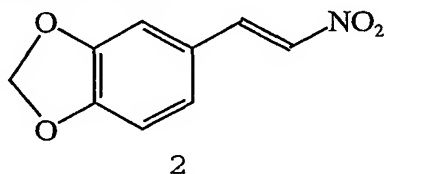


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X and Y are O and R₁ to R₃ are hydrogen (3,4-methylenedioxy-β-nitrostyrene)

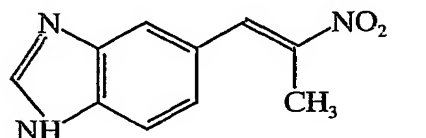
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2

X is N, Y is NH, R₁ is methyl and R₂ and R₃ are hydrogen
15 (benzimidazole-5-β-nitropropylene)

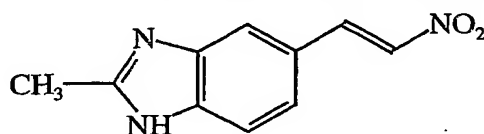
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3

X is N, Y is NH, R₁ is hydrogen, R₂ is methyl and R₃ is
absent (2-methyl benzimidazole-5-β-nitroethylene)

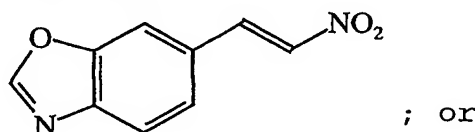
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4

30 X is O, Y is N, R₁ and R₂ are hydrogen and R₃ is absent
(benzoxazole-5-β-nitroethylene)

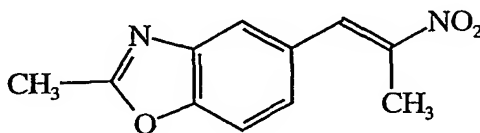
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- 29 -

X is N, Y is O, R₁ and R₂ are methyl and R₃ is absent (2-methyl benzoxazole-5-β-nitropropylene)



6

14. Use of the compound of formula I as defined in
10 any one of claims 1 to 13 in promoting growth of a
subject.

15. Use of the compound of formula I as defined in
any one of claims 1 to 13 in the manufacture of a
15 medicament or feed for promoting growth of a subject.

16. A compound of formula I as defined in any one of
claims 1 to 13 for use in promoting growth of a subject.

20 17. A composition for promoting growth in a subject,
which comprises the compound of formula I as defined in
any one of claims 1 to 13 and a carrier.

18. A pharmaceutical or veterinary composition
25 comprising the compound of formula I as defined in any one
of claims 1 to 13 and a pharmaceutically or veterinarily
acceptable carrier.

19. A composition according to claim 18 which is a
30 topical, oral or parenteral composition.

20. A composition according to claim 18 or claim 19
in which the pharmaceutically or veterinarily acceptable
carrier is an organic solvent.

35 21. A composition according to claim 20 in which the
organic solvent is acetone, benzene, acetonitrile, DMSO or

- 30 -

an alcohol.

22. A feed for promoting growth in a subject
comprising the compound of formula I as defined in any one
5 of claims 1 to 13.

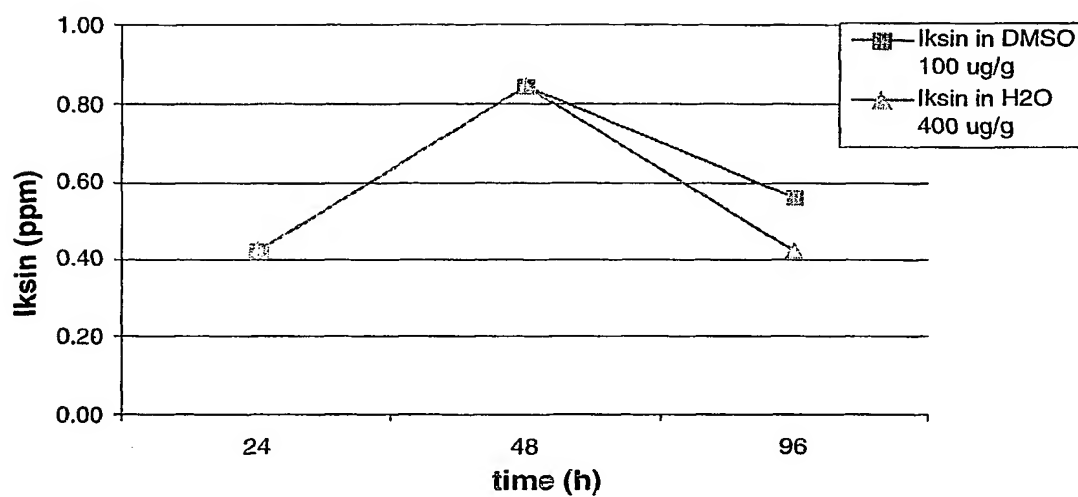
23. A feed according to claim 22 which further
comprises a carrier selected from alfalfa meal, soybean
meal, cottonseed oil meal, linseed oil meal, sodium
10 chloride, corn meal, cane molasses, urea, bone meal, fish
meal, corncob meal, calcium chloride and vegetable or
plant oil.

24. A growth promoting agent or nutritional
15 supplement comprising the compound of formula I as defined
in any one of claims 1 to 13.

25. Use of the compound of formula I as defined in
any one of claims 1 to 13 as a growth promoting agent or
20 nutritional supplement.

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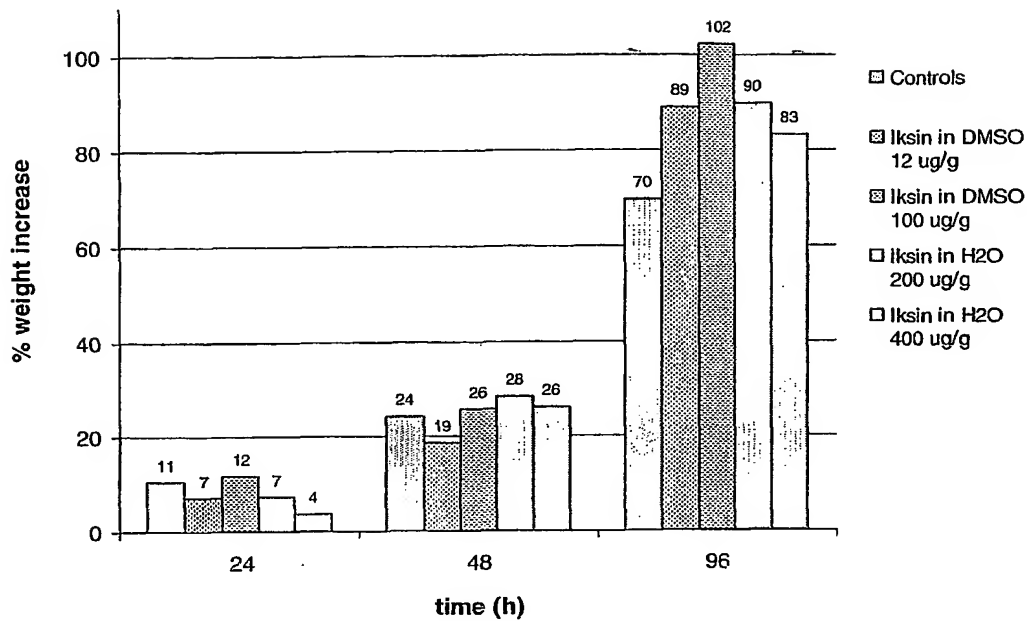
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Figure 1

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5

Figure 2

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/000253

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ⁷: C07D 235/10, 263/56, 317/50, 317/52, A61K 31/36, 31/4184, A61P 31/00, 31/04, 39/00.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Substructure based on 3,4 methylenedioxy, benzoxazole and benzimidazole nitrostyrene analogs for STN, Chemical Abstracts, WPIDS. Keywords: growth, anti, promot, anthel, animal.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2002/102789 A1 (BIODIEM LTD) 27 December 2002. See entire document.	1-25
Y	US 3962415 (C. HENNART et al) 8 June 1976. See entire document.	1-25
Y	Synthetic Communications, 1994, vol. 24(6), pages 819-832, R. P. K. Kodukulla et al, "Synthesis, chemical transformation and antimicrobial activity of a novel class of nitroolefins: 1,3-diaryl-2-nitroprop-1-enes." See especially table 2.	1-25



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent but published on or after the international filing date

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
17 March 2004

Date of mailing of the international search report

- 6 APR 2004

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2004/000253

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4469703 (A. KIS-TAMAS et al) 4 September 1984. See especially example 12 and table IV example 38.	1-25
Y	US 4463009 (W. J. SANDERS et al) 31 July 1984. See entire document.	1-25
Y	WO 2000/021381 (DSM N. V.) 20 April 2000. See entire document.	1-25
Y	The Veterinary Quarterly, 1987, vol. 9, no. 4, pages 309-320, H. L. DuPont et al, "The human health implication of the use of antimicrobial agents in animal feeds." See entire document.	1-25
Y	US 4948782 (S. OMURA et al) 14 August 1990. See entire document.	1-25

INTERNATIONAL SEARCH REPORT
Information on patent family members

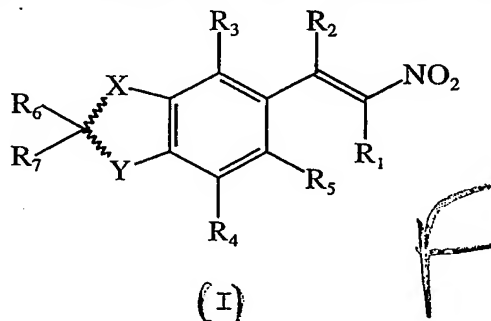
International application No.
PCT/AU2004/000253

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	2002102789	CA	2450121		
US	3962415	US	4058607		
US	4469703	AT	387480	AT	444782
		BE	884473	BG	35028
		CH	650244	DD	152272
		DE	3028357	DK	324480
		FR	2462416	GB	2054594
		IL	60586	JP	56086136
		PL	225900	SU	1264838
		AU	60789/80		
		BG	35035		
		DD	156079		
		ES	8105966		
		GR	69663		
		NL	8004203		
		YU	188180		
US	4463009				
WO	2000021381	AU	64730/99	BR	9914555
		CZ	20011328	EP	1121021
		HK	1030855	HU	0104001
		NL	1013308	NO	20011833
		PL	347250	SK	5022001
		CA	2346075		
		GB	2349794		
		ID	28812		
		NZ	510932		
		ZA	200102825		
US	4948782	CN	88101027	JP	64000023
END OF ANNEX					

ABSTRACT

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in which

X and Y are either the same or different and selected from a heteroatom;

(a) is a double or single bond depending on the heteroatoms X and Y;

R₁ to R₅ are either the same or different and selected from hydrogen or a non-deleterious substituent;

and

R₆ and R₇ are either the same or different and selected from hydrogen and a non-deleterious substituent or one of R₆ and R₇ are absent when there is a double bond present,

pharmaceutically or veterinarily acceptable salts or derivatives, pro-drugs, tautomers and/or isomers thereof to a subject in need thereof.

F for scanning

10/527033

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2004/000253

A. CLASSIFICATION OF SUBJECT MATTER

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Date of the actual completion of the international search
17 March 2004

Date of mailing of the international search report

- 6 APR 2004

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2004/000253

/C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4469703 (A. KIS-TAMAS et al) 4 September 1984. See especially example 12 and table IV example 38.	1-25
Y	US 4463009 (W. J. SANDERS et al) 31 July 1984. See entire document.	1-25
Y	WO 2000/021381 (DSM N. V.) 20 April 2000. See entire document.	1-25
Y	The Veterinary Quarterly, 1987, vol. 9, no. 4, pages 309-320, H. L. DuPont et al, "The human health implication of the use of antimicrobial agents in animal feeds." See entire document.	1-25
Y	US 4948782 (S. OMURA et al) 14 August 1990. See entire document.	1-25

INTERNATIONAL SEARCH REPORT
Information on patent family members

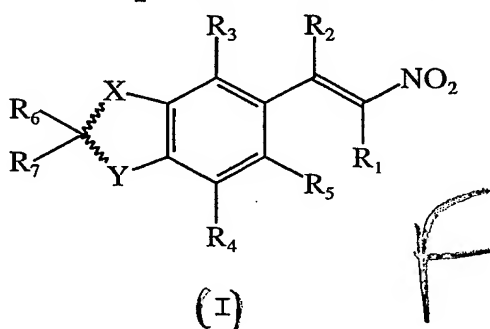
International application No.
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	2002102789	CA	2450121		
US	3962415	US	4058607		
US	4469703	AT	387480	AT	444782
		BE	884473	BG	35028
		CH	650244	DD	152272
		DE	3028357	DK	324480
		FR	2462416	GB	2054594
		IL	60586	JP	56086136
		PL	225900	SU	1264838
				AU	60789/80
				BG	35035
				DD	156079
				ES	8105966
				GR	69663
				NL	8004203
				YU	188180
US	4463009				
WO	2000021381	AU	64730/99	BR	9914555
		CZ	20011328	EP	1121021
		HK	1030855	HU	0104001
		NL	1013308	NO	20011833
		PL	347250	SK	5022001
				CA	2346075
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				ID	28812
				NZ	510932
				ZA	200102825
US	4948782	CN	88101027	JP	64000023
END OF ANNEX					

ABSTRACT

The present invention relates to a method of promoting growth comprising the step of administering an effective amount of a compound of formula I:



in which

X and Y are either the same or different and selected from a heteroatom;

(a) is a double or single bond depending on the heteroatoms X and Y;

R₁ to R₅ are either the same or different and selected from hydrogen or a non-deleterious substituent; and

R₆ and R₇ are either the same or different and selected from hydrogen and a non-deleterious substituent or one of R₆ and R₇ are absent when there is a double bond present,

pharmaceutically or veterinarily acceptable salts or derivatives, pro-drugs, tautomers and/or isomers thereof to a subject in need thereof.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2004/000253

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ⁷: C07D 235/10, 263/56, 317/50, 317/52, A61K 31/36, 31/4184, A61P 31/00, 31/04, 39/00.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Substructure based on 3,4 methylenedioxy, benzoxazole and benzimidazole nitrostyrene analogs for STN, Chemical Abstracts, WPIDS. Keywords: growth, anti, promot, anthel, animal.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2002/102789 A1 (BIODIEM LTD) 27 December 2002. See entire document.	1-25
Y	US 3962415 (C. HENNART et al) 8 June 1976. See entire document.	1-25
Y	Synthetic Communications, 1994, vol. 24(6), pages 819-832, R. P. K. Kodukulla et al, "Synthesis, chemical transformation and antimicrobial activity of a novel class of nitroolefins: 1,3-diaryl-2-nitroprop-1-enes." See especially table 2.	1-25

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 17 March 2004	Date of mailing of the international search report - 6 APR 2004
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929	Authorized officer FRANCES RODEN Telephone No : (02) 6283 2239

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